Review

Clear Cell Papillary Renal Cell Carcinoma – A New Emerging Entity

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Clear cell papillary renal cell carcinoma was initially reported in patients with end stage renal disease under name of "end stage renal disease-associated renal cell carcinoma". However, subsequent studies show that the tumor is also seen in non-end stage settings with or without impaired renal function. Recent advances in molecular genetic techniques and immunohistochemical staining have showed that clear cell papillary renal cell carcinoma is a new distinct entity that has unique genetic, histomorphological and clinical characteristics. This review summarizes the most current views on clear cell papillary renal cell carcinoma with focus on histomorphological features, immunohistochemical profiles and molecular genetic characteristic of this new entity.
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INTRODUCTION

The first renal neoplasm was reported nearly 200 years ago.[1] Clear cell renal cell carcinoma accounts for 60-70% of all cases of renal cell carcinoma and papillary renal cell carcinoma comprises approximately 10% of renal cell carcinoma.[2-3] Tumors arising in kidneys involved by end stage renal diseases may show distinctive histologic features not easily classified according to the current World Health Organization (WHO) classification System.[3-5] Tickoo et al described 15 cases of "clear-cell papillary renal cell carcinoma of end stage kidneys," which were mainly cystic tumors and showed prominent papillary architecture with purely clear-cell cytology.[5] An association with end-stage renal disease was initially described for clear-cell papillary renal cell carcinoma, but many cases have now been documented outside of this setting.[6] This newly described low grade entity has been given many names such as "renal angiomyoadenomatous tumor", "clear cell tubulopapillary renal cell carcinoma" and "clear cell papillary renal cell carcinoma".[7-9] The nomenclature was discussed at the recent annual meeting of United States and Canadian Association of Pathologists (USCAP, 2011) and the name of "clear cell papillary renal cell carcinoma" was adopted.[10-11]

HISTOMORPHOLOGIC FEATURES OF CCPRCC

Recently, three cases of clear cell papillary renal cell carcinoma were seen at our institution. Grossly, these tumors are well circumscribed and encapsulated with tan-pink to tan-red, cystic cut surfaces. The tumors are localized to the renal cortex without any infiltration into the perirenal or renal sinus fat (**Figure 1a**). Tumor sizes range from 1.3 to 3.8 cm., similar to those described in the literature in which 5 cases reported by Gobbo et al are pT1 tumors (less than 7 cm).[9] Similarly, another paper studied 36 cases of such tumors and found that 34 were T1a (less than 4 cm) and 2 were T1b (betwenn 4 and 7 cm).[8]

Histologically, all of our three cases show tumor is surrounded by a thin fibrous capsule and is composed of predominantly tubulopapillary components with varying degree of cystic areas. The papillae are lined by medium sized cuboidal cells with abundant clear cytoplasm. The tumor cells exhibit nuclei arranged toward the luminal surface, a characteristic feature of CCPRCC. All of the tumors were Fuhrman nuclear grade 2, consistent with that of previous reports (**Figure 1**).[8-12] No mitotic figures, foamy macrophages, calcifications, necrosis or sarcomatoid differentiation is identified. Lymphovascular invasion is absent.

Aydin et al found that in 92% (33/36) of CCPRCC, cysts of different sizes are present and often contain serosanguinous fluid or colloid-like secretions. In 97% (35/36) of tumors, tubules and acini of variable size and shape are also present. The cystic wall is lined by a single layer of cells with scant eosinophilic cytoplasm or a moderate amount of clear cytoplasm.[8] Rohan et al suggest that conspicuous nuclear positioning away from the basement membrane is one of the unique features of CCPRCC.[13] In addition, smooth muscle fibers are often found at least focally in 69% of CCPRCC.[8] Furthermore, in contrast to classic clear cell renal cell

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carcinoma, CCPRCC lacks a delicate sinusoidal vascular network.[9]

If one is not aware of this new entity, CCPRCC can be confused morphologically with other renal cell carcinomas, particularly clear cell carcinoma or papillary carcinoma and their variants. However, conventional clear cell RCC and papillary RCC often exhibit more aggressive pathologic features, including larger tumor size, higher Fuhrman grade nuclei (3 and 4), coagulative necrosis, perirenal fat involvement, vascular invasion, lymph node metastasis, and sarcomatoid differentiation. None of these are seen in CCPRCC.[14] Occasionally, however, immunohistochemistry studies may be needed for definitive classification.

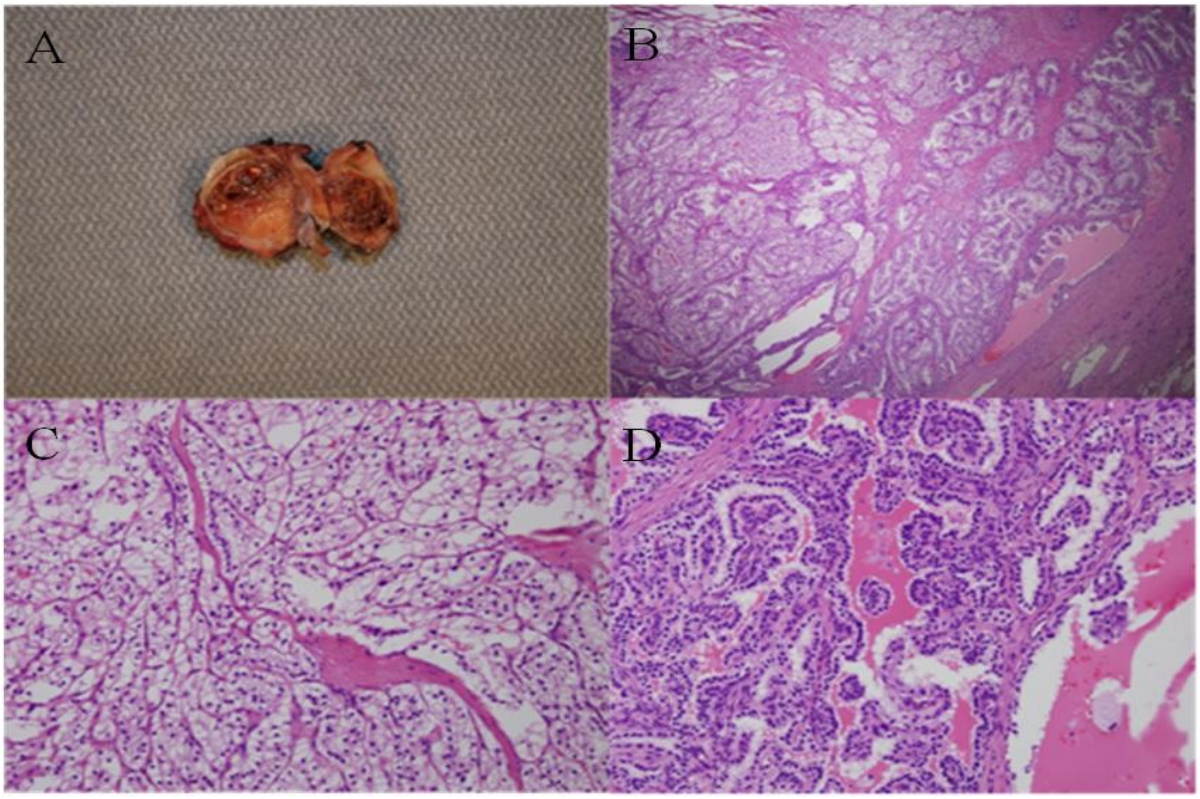

Figure 1. A. Gross image of clear cell papillary renal cell carcinoma. Tumor is well circumscribed and encapsulated with tan-pink to tan-red cut surface. A cystic area is also evident. **B**. At low power view, the tumor is tubulopapillary with microcysts. **C** and **D**. At higher power view, the tumor has a nested and papillary patterns. Tumor cells have abundant cytoplasm, low grade nuclei and nuclei located away from the basement membrane.

IMMUNOHISTOCHEMISTRY PROFILES OF CCPRCC

CCPRCC has a distinctive immunoprofile. Gobbo et al found that all tumors show strong and diffuse positive immunohistochemical staining for cytokeratin 7 and carbonic anhydrase IX. The tumor cells are negative for alpha-methylacyl-CoA racemase (AMACR), CD10, and transcription factor E3.[6] Another study reported that most tumors are negative for CD10 except few are focally positive with expression limited to 1-10% of the tumor cells.[8] This study also found that staining for TFE3 protein, a distinctive and diagnostic feature of Xp11.2 translocation RCC, was not identified in any of their tumors.[15,16] Conventional clear cell renal cell carcinomas typically show immunoreactivity to antibodies against CA-IX and CD10 and lack immunoreactivity for CK7.[17-19] Papillary renal cell carcinomas characteristically show positive immunostaining for AMACR and CK7,[17-20] but less frequently express CA-IX and/or CD10.[21] Also of note, Xp11.2 translocation associated renal cell carcinomas do not express CK7 and usually show positive immunostaining for CD10.[16] In addition to CA IX, another study evaluated immunoexpression of two other markers of HIF pathway activation, HIF-1α and GLUT-1. The majority of CCPRCC express both of these markers as clear cell renal cell carcinoma does.[13] In addition, Wolfe et al reported focal to abundant disorganized bundles of spindle cells with eosinophilic cytoplasm and cigar-shaped nuclei that expressed desmin and h-caldesmon, consistent with smooth muscle in 4 out of 4 cases.[22]

In our recent cases, immunohistochemical studies were performed. As iilustrated in **Figure 2**, tumor cells are strongly and diffusely positive for CK7, PAX-2 and vimentin. Immunostain for high molecular weight cytokeratin was focally positive. Tumor cells are negative for AMACR and CD10 (**Figure 2**).

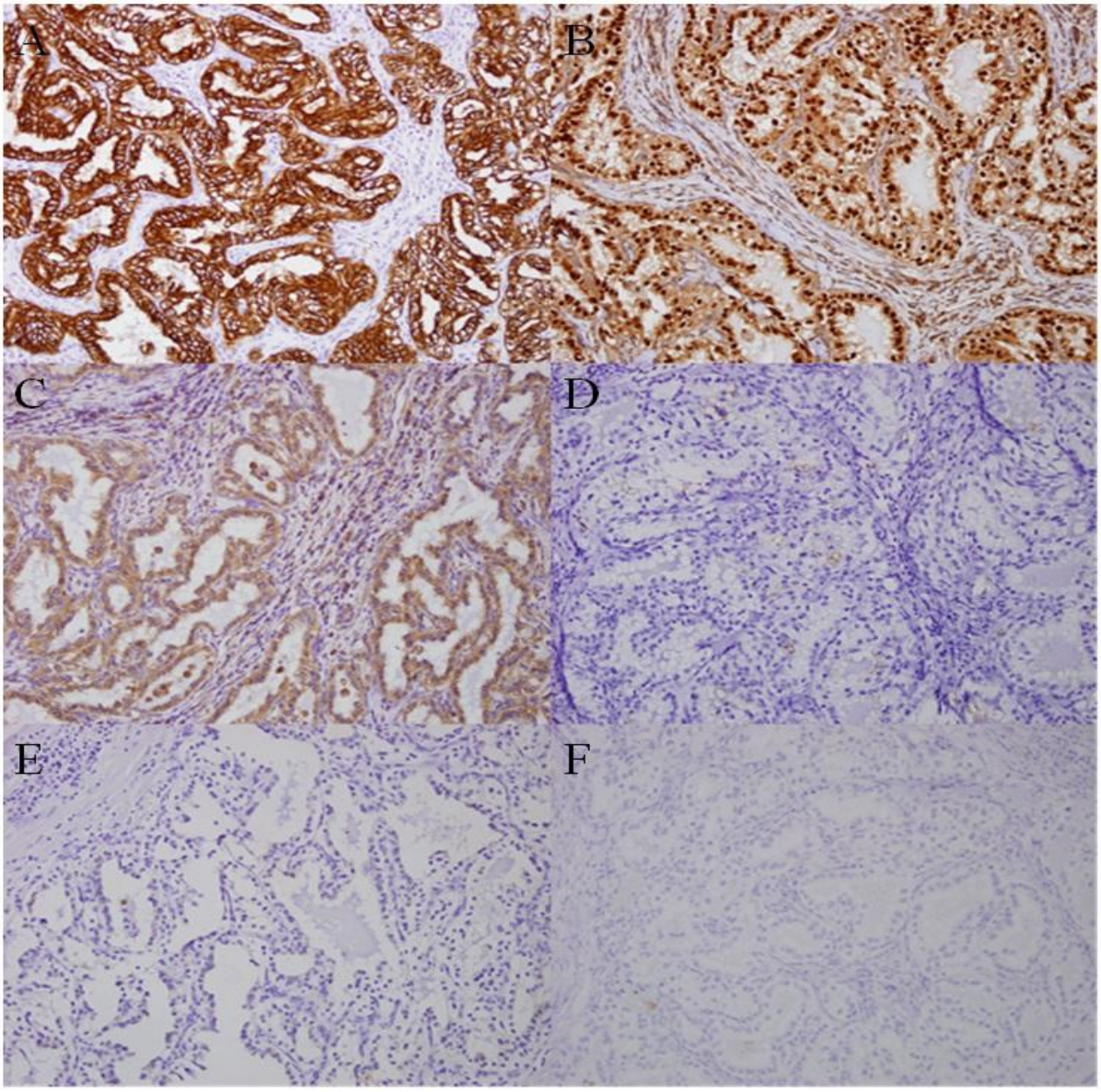

Figure 2. Immunohistochemical studies of CCPRCC. **A.** CK7; **B.** PAX-2; **C.** Vimentin; **D.** High molecular weight cytokeratin; **E.** CD10; **F.** Racemase.

MOLECULAR GENETIC CHARACTERISTICS OF CCPRCC

The genetic abnormalities of several types of renal cell carcinomas have been well described. Clear cell renal carcinoma often has deletions in chromosome 3p and /or mutations in VHL genes, while papillary renal cell carcinoma often has a trisomy of chromosomes 7 or 17 and loss of the Y chromosome.[3] Aydin et al, found that none of the 36 cases of CCPRCC display gains of chromosome 7 or loss of Y chromosome, a typical feature of papillary renal cell carcinoma (PRCC), and none of the cases has deletion of 3p a typical feature of clear cell renal cell carcinoma (CCRCC).[8] Another study showed monoclonal gains of chromosomes 7, 10 and 12 which were detected in one case of CCPRCC, and their presence was verified by fluorescence in situ hybridization (FISH) studies.[22] On the other hand, Michel et al found Trisomy 7 together with monosomy 17, 16 and 20 in one case of CCPRCC. Trisomy 17 was seen in another case of CCPRCC. No other chromosomal gains or losses were found.[7] In addition, Gobbo et al reported in contrast to the control cases of clear cell RCC and papillary RCC, 3p deletion was not observed in any case of CCPRCC. Furthermore, chromosomes 7 and Y were numerically normal in all of their cases and only 1 of 5 cases showed gain of chromosome 17.[7] Using quantitative RT-PCR approach, Rohan et al showed relative over expression of *VHL* mRNA in CCPRCC compared with non-neoplastic renal parenchyma and clear cell RCC cases harboring 3p losses andor *VHL* mutations. These finding supports the notion that the molecular mechanism underlying CCPRCC is distinct from that of clear cell RCC or papillary RCC and is not related to abrogation of *VHL* signaling.[7]

SUMMARY

CCPRCC is a new entity described since the 2004 World Health Organization classification of renal tumors. Due to its unique histomorphology, immunohistochemical staining pattern, molecular genetic features and favorable clinical outcome, CCPRCC deserves a separate entity and will be included in the newer edition of WHO classification of renal tumors. Anecdotally, the authors feel that CCPRCC is not as rare as one may expect since we have seen three immunohistochemically proven cases in a few months in our institution. We feel that pathologists need to be aware of this new entity. The morphology and immunohistochemical staining pattern is quite characteristic of this tumor, and it is relatively easy to confirm the diagnosis. It is worth noting that recognizing this entity is important as its prognosis is much better than that of both clear cell RCC and papillary RCC. No recurrence, lymph node or other metastases have been reported to date for CCPRCC.

CONFLICT OF INTEREST

The authors have no conflict of interest to disclose.

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